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13. ABSTRACT (Maximum 200 Words)

The purpose of this research is to investigate whether eating brown seaweed (*Undaria pinnatifida*) and soy powder can influence hormone levels that are thought to affect breast cancer risk. Brown seaweeds and soy foods are popular in Japan, where the incidence of breast cancer is about 1/6 the rate of that reported for American women. In several animal studies of diet and cancer, adding seaweed or soy to the normal diet resulted in longer healthy lives. Many studies have found that soy consumption in Asia appears to be linked directly to lower breast cancer risk, and laboratory studies have confirmed that soy reduces tumors in animal models. Constituents of soy have been proposed as antiestrogens and antioxidants, may induce apoptosis and angiogenesis (Zheng, 1999). We want to investigate how eating seaweed and soy together might affect hormone levels predictive of women's health. We will use commercially available seaweed and soy powder. These seaweeds and soy powder are commonly found in health food stores.

To date, the only progress that has been made is to obtain approval from HSRRB (Proposal Log Number BC972552, HSRRB Log Number A-8050), with modifications. Modifications were submitted October 2, 2002. Final approval has not yet been granted.

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Introduction

The purpose of this research is to investigate whether eating brown seaweed (*Undaria pinnatifida*) and soy powder can influence hormone levels that are thought to affect breast cancer risk. Brown seaweeds and soy foods are popular in Japan, where the incidence of breast cancer is about 1/6 the rate of that reported for American women. In several animal studies of diet and cancer, adding seaweed or soy to the normal diet resulted in longer healthy lives. Many studies have found that soy consumption in Asia appears to be linked directly to lower breast cancer risk, and laboratory studies have confirmed that soy reduces tumors in animal models. Constituents of soy have been proposed as antiestrogens and antioxidants, may induce apoptosis and angiogenesis. We want to investigate how eating seaweed and soy together might affect hormone levels predictive of women's health. We will use commercially available seaweed and soy powder. These seaweeds and soy powder are commonly found in health food stores

Body

Research Accomplishments

To date, I have made numerous revisions to the Informed Consent and Protocol. Although it was approved with modification in August 2002, and the final modifications were submitted in October 2002, it has not yet been given final approval.

Since so much time has passed since I first wrote this grant, preliminary results from our two other studies are now available. Based on the new information, a request for revisions to the grant and to the scope of work have now been submitted to Dr. Donna Kimbark. Once these changes are approved, the revised Informed Consent and Protocol will be submitted to the HSSRB.

Reportable Outcomes

HSSRB final approval has almost been obtained.

Conclusions

None yet.

References

None.

Appendices

Modifications to this grant as they have been submitted to Dr. Donna Kimbark. Grants Manager
Congressionally Directed Medical Research Programs
Breast Cancer Research Program

Appendices

Modifications to the Scope of Work that have been submitted to
Dr. Donna Kimbark, Grants Manager, Congressionally Directed Medical Research Programs
Breast Cancer Research Program
1077 Patchel Street, Fort Detrick
Frederick, MD 21702

Scope of Work Revision

DAMD17-98-1-8207
Dietary Seaweed and Early Breast Cancer: A Randomized Trial

1. The goal of this grant has been to identify ways that seaweed could prevent breast cancer. Epidemiologic studies comparing breast cancer rates among Japanese women in Japan and American women in the US are supportive that dietary factors could be critical to understanding breast cancer rates. In vitro work using seaweed extracts have shown high antitumor activity. In vivo work using rats and mice have demonstrated that seaweed, both as part of a regular diet or extract in drinking water and as extracts which were injected into tumor bearing rats, have all confirmed that seaweeds inhibit cancer formation and can cause tumor remission/tumor rejection in animals. Table 1 presents the data on dietary seaweed and mammary tumors in animals.
2. This grant was originally to study the effects of dose of dietary seaweed, as measured by duration of seaweed consumption, on estradiol, estrone, sex hormone binding globulin, phytoestrogen metabolism, and thyroid hormone metabolism. I modified it to include 6 weeks of placebo or seaweed plus one week of placebo plus soy or one week of seaweed plus soy. These endpoints reflected my thinking at the time and the state of knowledge at the time. Since then, I have completed a preliminary study funded by the Susan G. Komen Foundation, and have re-thought these endpoints. Table 2 presents our results of that study.
3. Based on the results in Table 2, soy appears to exert the predominant influence on these endpoints, and seaweed, if anything, appears to blunt the response of soy, except for equol and genistein. For these phytoestrogens, the combination of seaweed and soy had a significant enhancing effect. In both cases, seaweed increased excretion. For equol, the phytoestrogen considered most protective against breast cancer, and is thought to be synthesized in the colon. However, only about 30-35% Americans seem able to produce equol (Setchell, 2003). In any case, the goal of my original grant was to explore the possibility that seaweed could prevent breast cancer, not that seaweed could modify and enhance the breast cancer risk influences of soy. I would therefore like to drop soy from this study, and concentrate on the mechanisms by which seaweed could exert a protective effect in breast cancer etiology.
4. The difficulty has been to identify the critical pathways important in breast cancer and in the metabolism of seaweed. In our preliminary study of chronic seaweed ingestion in healthy postmenopausal women provides insights into which pathways are non-responsive dietary seaweed. In the study of the effects of chronic 6-week ingestion of 5 grams of seaweed showed that seaweed did not affect sex hormone levels (circulating serum estrogen levels, sex hormone binding globulin, phytoestrogen excretion, estrogen catabolism (2 hydroxyestrone and 16 α-hydroxyestrone ratio). Thyroid stimulating hormone did increase, although all subject values were within normal TSH range. As would be expected from 500-ug/d additional iodine from the seaweed, urinary iodine excretion increased.

However, relevance of these changes is unclear in breast cancer etiology. Urinary excretion of melatonin did increase in women while taking the seaweed supplements, but it was a statistically significant increase only for women who had never had breast cancer. In addition, there was no change in serum carotenoids, insulin like growth factor-1, insulin like growth factor binding protein 3, or in homocysteine.

5. Results from our preliminary study of the acute effects of seaweed, measured before and 4 hours after consuming 5 grams of seaweed with a high fat breakfast from McDonalds (sausage biscuit, hash browns, orange juice, and coffee) showed no changes in cholesterol, lipids (triglycerides, HDL), beta hydroxybutyrate, liver fatty acid binding protein, glucose, leptin, L-selectin, and neurotensin. Although LDL in December was on average 17 mg/dL lower with seaweed than with placebo, in a repeat of the study in May, there were no differences. This could reflect variation in the seaweed used (early versus late harvest) or it could reflect seasonal differences in lipid response to dietary fat.
6. We also measured tumor necrosis factor alpha, as an indication of innate immunity changes. Although there was no change for the eight healthy people, there was a 23% increase (11 pg/ml) for one person with an active oral abscess. Table 3 presents data on other studies that have used seaweed and human lymphocytes. It seems likely that seaweed would enhance immune response in the presence of an immune challenge.
7. We also measured P-selectin, a platelet cell adhesion molecules. A significant change in P-selectin was detected by flow cytometry. The amount of bound P-selectin remained stable, but the amount of free P-selectin increased significantly. Figure 1 presents these results: As our only measured change with seaweed supplementation, it is also the one most consistent with reported seaweed antitumor activity and with a wide range of data on fucoidan, the sulfated polysaccharide only found in brown seaweeds.
8. Fucoidan and heparin have similar properties. They are long branched chains of sulfated sugars. Depending on the species of seaweed, fucose can make up 90% of the sugars, although in *Undaria*, the seaweed we will be using, it is roughly 50%fucose and 50% galactose. Fucoidans have been widely studied for inhibition of cell rolling and cell tethering. This is a critical requirement for cell-cell adhesion. Current evidence supports the idea that tumor cells attach via selectins to platelets. By forming clusters of platelets around a tumor cell, the tumor cell is thought to escape recognition by the host immune cells. When the tumor cell-platelet cluster attaches to an endothelial wall, tumor cells are thought to extravasate through the vessel wall to establish new metastatic cancer site. The evidence for this comes from *in vitro* work and *in vivo* studies that demonstrate inhibiting P-selectin can decrease metastasis. Borsig (2002) reviews these data in two recent PNAS articles.
9. A sugar-related therapy Bimosiamose, made by Texas Biotechnology, is a drug developed to inhibit selectins on blood walls. It is currently in a phase II trial for asthma and psoriasis. Interestingly, our pilot study included two women who had psoriasis, and both reported that taking seaweed provided symptomatic relief from their psoriasis.

10. One of the problems with replicating the initial study using a different seaweed. Our preliminary study used an American seaweed, *Alaria esculenta*, but we decided to use *Undaria pinnatifida* from Tasmania, Australia, after visiting their harvesting site and processing plant. This is primarily because the *Undaria* is specifically harvested when the high fucoidan-containing sporophyll is mature, and the dried seaweed is assayed for fucoidan content. This is in contrast to the *Alaria*, which specifically does not include the sporophyll, and is not assayed for fucoidan content. In addition, the iodine content of *Undaria* is half of that in *Alaria*. And finally, three of the four animal studies of mammary carcinoma inhibition in animals have used *Undaria* (see Table 2).
11. We would also be recruiting a more racially diverse subject population in South Carolina, compared with the all white population in central Massachusetts. However, we would again be studying healthy women.
12. If we consider that seaweed can enhance the immune response to pathogens and inhibit tumor metastasis, but not have any harmful side effects, then it should not cause any perturbations in the immune system of healthy women. The three people who had health challenges (the two with psoriasis and the one with the tooth abscess) provide additional insights into seaweed activity, and could be explained by increasing innate immune response (the TNFα) and decrease in psoriasis symptoms with decrease in P-selectin binding. Using the P-selectin data from the McDonald's breakfast study, it is very likely that the high fat meal was a challenge to the body, and that seaweed diminished the harmful platelet aggregation activity resulting from a high fat meal. However, studying healthy women on normal diets will almost certainly not show any differences with or without seaweed.
13. Our data suggest that seaweed is non-toxic and non-stimulating to healthy people.
14. We would like to propose that the intent of this IDEA Award was to investigate how seaweed could prevent breast cancer, and that to best study this, we need to look in greater depth at modulation of cell-cell adhesion. This is best done by studying the effects of dietary seaweed in three populations: one group of healthy women, one group who has had early breast cancer (Stage I or II) and is currently disease free, and one group who has had locally advanced (Stage III) breast cancer. Additionally, since the effect of seaweed on P-selectin was seen within 4 hours, there is no need to have an 18-week study. Based on animal data showing enhancement of T cells and possibly B cells after seaweed therapy, and knowing that it takes at least a week for the body to mount a T or B cell defense against an antigen, we propose that a six-week study would be sufficient. This would be a randomized double-blinded crossover study that includes 2 weeks on 5-grams/d seaweed, 2 weeks washout period (taking 5 g/d placebo), and 2 weeks of 5-g/d placebo.
15. The immune response is a complicated series of pathways, all likely to be regulated in different people at slightly different rates. It would be ideal to use a DNA microarray approach to identifying patterns of gene expression encoding for cell adhesion and innate and adaptive immune response. By creating a microarray of genes specifically regulating cell adhesion, and immune response, based on known seaweed – induced modulation *in vitro* and *in vivo*, we will be able to detect changes in gene expression that might not yet be manifest in serum protein markers. This approach will also allow us to investigate the interrelationships between gene regulation that may be important in breast cancer surveillance and tumor responses. Once genes of interest have been

identified by the microarray analysis, we would use the stored serum to do ELISA assays to test for the presence of serum proteins associated with these genes.

16. To do this, we would recruit 15 women (5 healthy women, 5 who have been treated for early breast cancer but are currently disease free, and 5 women who have been treated for Stage III breast cancer but are currently not receiving treatment and are considered at high risk for recurrence). The 15 women would be randomized to seaweed or placebo first, have their blood drawn at baseline, take 5 g/d (10 capsules) of *Undaria pinnatifida* or placebo for 2 weeks, have their blood drawn again, and take placebo for two week washout period, have their blood drawn and take 10 capsules of placebo or *Undaria* (which ever not taken the first time) for 2 weeks, and have their blood drawn again. Altogether we would have 4 time points. The DNA microarray analysis would be done only after 2 weeks on placebo and 2 weeks on *Undaria*. In addition to the blood needed for the DNA microarray, the blood samples from the 4 visits would be collected, centrifuged, and 1 ml aliquots of serum would be stored at –80. These samples would be used in ELISA assays once a gene of particular interest has been identified.
17. Summary of changes:

Original study	**Revised study**
40 women	**15 women**
20 Healthy women	**5 Healthy women**
20 women who have had Stage I/II breast cancer	**5 women who have had Stage I/II breast cancer** **5 women who have had Stage III breast cancer**
18-week study	**6-week study**
9 blood draws	**4 blood draws**
Estrogen, phytoestrogen, thyroid hormones Melatonin endpoints	**DNA microarray with ELISA assays for proteins associated with genes that show up/down regulation by seaweed**
24 hour urine collection (9 days)	**No urine collection**
Included two weeks of soy supplementation	**No soy**

18. If these study modifications are approved, the first 2 months will be devoted to identifying 333 genes to be used in the microarray slide, and contracting for the custom microarray slide. Then 6 months to recruit the 15 women and to collect data, 1 year to complete microarray and ELISA assay, and 6 months to write papers for publication.
19. Dawen Xie, Ph.D. will be the co-PI on this study. Dr. Xie is an expert in DNA microarray analysis. All DNA microarray and ELISA assays will be done in his lab.

Revised Scope of Work

2 months
Microarray chip development

6 months
Subject recruitment and study participation

12 months
Microarray and ELISA analysis

6 months
Data analysis

Table 1. Pilot study results of seaweed and soy on breast cancer risk factors for 23 women excluding Tamoxifen and antibiotic users

	Seaweed			Soy		
	Mean	SE	P value	Mean	SE	P value
Estrogens						
E1						
Breast Cancer	1.5	2.7	.54	-1.9	2.7	.44
Disease Free	1.4	1.4	.91	1.0	1.4	.47
E2	0.2	1.9	.91	-1.7	1.9	.39
SHBG	-0.9	1.7	.62	-7.1	1.7	**.0001**
Thyroid function						
T3	3.6	2.5	.15	0.9	2.5	.71
T4	0.05	.16	.72	0.1	.16	.40
THBR	-0.01	.01	.48	-0.01	.01	.32
FTI	0.03	.14	.82	0.19	.14	.18
TSH	0.5	.11	**.0001**	0.2	.11	**.03**
Iodine (urinary)	315	30	**.001**	297	30	**.0001**
Phytoestrogens (log transformed)						
Daidzein	0.02	.45	.96	5.1	.45	**.001**
Glycitein	-0.3	.47	.52	5.4	.47	**.0001**
Equol	-.39	1.1	.71	3.9	1.1	**.001**
Genistein	-0.8	.68	.23	5.9	.68	**.0001**
DMA	0.2	.65	.72	7.7	.65	**.0001**
Seco (Untransformed)	-8.2	7.6	.29	0.9	7.6	.90
Enterodiol	0.04	.21	.83	-0.41	.31	.06
MAT	-0.3	.45	.47	-0.6	.45	.16
Enterlactone	-76.8	189.1	.69	-181.5	189.1	.34

Table 2. Animal studies of seaweed and mammary tumor inhibition.

Author control)	Study	Groups	Biomarkers (treated vs.
Funahashi, 1999 response)	DMBA in rats	0, 1%, 5% *Undaria*	↓ tumor (dose
	20 mg/body fed *Undaria* after 1 cm tumor dev	N=11/gr 8 wk post tumor	↑ T4 ~ = ↑ serum iodine (dose response) ~ =thyroid wt ↓BrdU* ↑TGF-β** (dose response) ↑Apoptosis*** (highest for 1%) wt gain > in 1%

*BrdU bromodeoxyuridine, a molecular marker to tumor proliferation. Mammary tumors injected sc with BrdUrd, then anti-BrdU antibody. Specimens were stained by streptavidin-biotin-peroxidase complex. Average of 4 fields of 1000 cells used for labeling index.
**Transforming growth factor, a negative growth factor in breast tumor cells. Specimens stained with streptavidin-biotin-peroxidase and then with phosphate-buffered saline (PBS) as a negative control. Four fields of 1000 cells averaged for labeling index.
***Apoptosis measured by TUNEL (TdT-mediated dUTP-biotin nick-end labeling). Index was average number of dead cells/1000 cell for four random visual fields.

Authors control)	Study	Groups	Biomarkers (treated vs.
Funahashi, 2001 100%)	DMBA in rats	n=12/g	↓ tumor incidence (24% vs.
In vivo	20 mg/100g mekabu in distilled water at 4°C for 24 hr then used as drinking water**	One wk post DMBA 32 wk study	↓ # tumor/rat (2 vs. 7) ↓ tumor diameter (100 mm^2 vs. 5400 mm^2)
In vitro	MCF-7 MDA-MB-231 T-47D	1 g mekabu/150 ml water	No change for normal cells 60% apoptosis at 24 hrs Apoptosis* at 24 and 72 hr
	MCF-10A (normal) Compared to 5-FU	MCF-7	30% at 24 hrs, 60% at 72 hrs (> than 5 FU at 72 hrs, $p<0.01$)
		MDA-MB-231	70% at 24 hrs, 75% at 72 hrs (> 5 FU at 24 and 72 hrs, $p<0.01$)
		T-47D	62% at 24 hrs, 70% at 72 hrs (> 5 FU at 24 and 72 hrs, $p<0.01$)

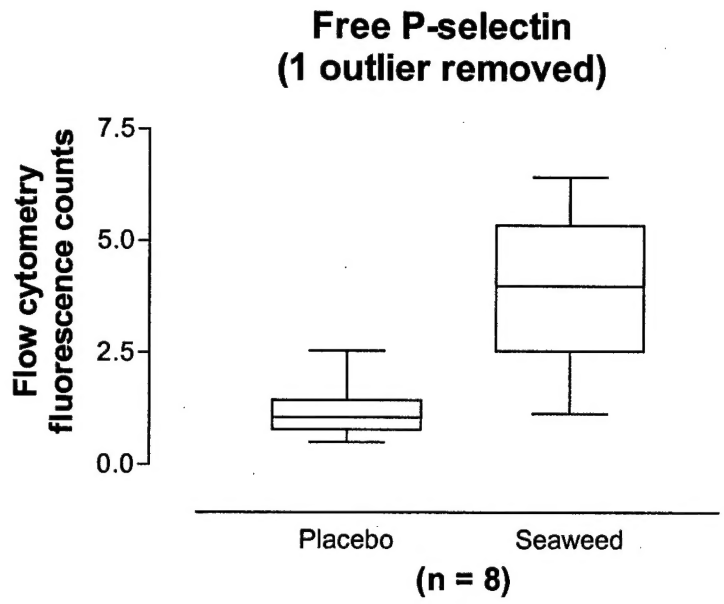
	MCF-10A	No change (normal cells)

* Apoptosis measured by flow cytometry.
** rats drank 27 ml water/day, average wt 250 g
Comparable dose in humans = 7 gm/d
In vitro 1 g mekabu solution about equal in apoptotic activity as 2 g, and significantly higher than 0.5 g.

Author	**Study**	**Groups**	**Biomarkers (treated vs. control)**
Yamamoto, 1987	DMBA rats	n=154 6 kinds of seaweed 2% seaweed in diet 20 mg DMBA seaweed given during DMBA, seaweed Supplementation Stopped 59 days before End of 211-day study	↓tumor incidence ↓ tumor weight ($p < 0.02$) ↑ time to 1st tumor ($p<0.01$)

Author	**Study**	**Groups**	**Biomarkers (treated vs. control)**
Teas, 1984	DMBA rats	n= 108 5 mg DMBA 5% Laminaria from 21 d until 182 d post DMBA (fasted overnight before DMBA)	↑ time to 1st tumor ($p=0.007$) ↓ # tumor/tumor bearing rat $p< 0.05$)

Figure 1. Comparison of placebo and seaweed on P-selectin as measured by flow cytometry



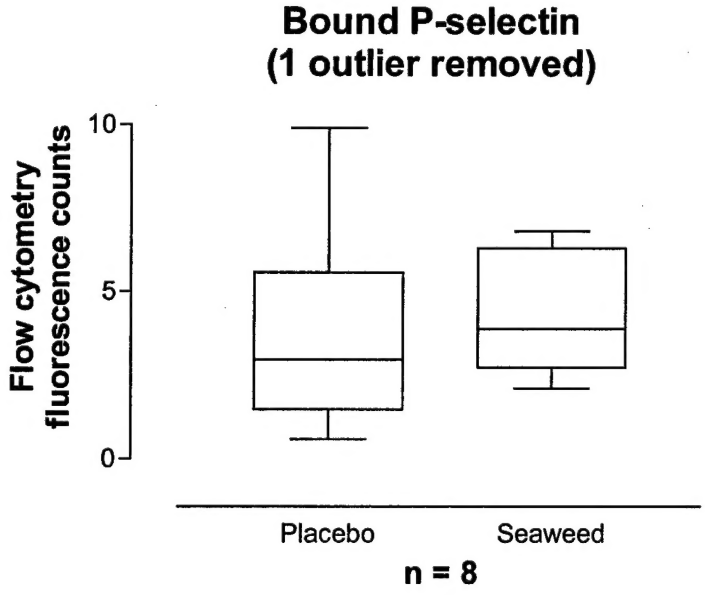


Table 3. Seaweed and immunity (studies that used human cells)

Author	Study	Groups	Biomarkers (treated vs. control)
Liu, 1997	B cell stimulation by seaweed	C3H/HeN mice C3H/HeJ mice	↑ proliferation of mouse spleen cells ($p < 0.05$) ^{3}H-TdR uptake (cpm)
In vitro	1 g Undaria/100ml Warm water for 1 hr; 50 x dilution after Millipore filtration	spleen cells 3 day incubation	(responders B cells not T cells) (not due to LPS)
			↑ Ig production ($p < 0.05$)
			↑ TNF production by macrophages 4-fold increase in L929 cell cytotoxicity, $p < 0.05$
		Human lymphocytes	↑ Human PBL cultured with *Undaria* For 3 days vs. control; ^{3}H-TdR upta Significantly ↑ for 1 of 3 cases

Author	Study	Groups	Biomarkers (treated vs. control)
Cooper, 2002			
In vivo	Herpes	21 Patients	↑ healing of active lesions No reactivation of latent infections
In vitro	T cells	1 g boiled with 40 ml water for 5 min, filtered, dried	
		Human T cells Cr uptake assay 72 hr	↑ proliferation T cells 25 ug/ml was 50% as effective as PHA and ConA
			No effect on NK cell activity
			No effect on L929 fibroblast growth

Author	Study	Groups	Biomarkers (treated vs. control)
Shan, 1999	Immune changes	**Human lymphocytes**	= to control for CTL, NK
	With seaweed	1 g dried seaweed	↑ IgG ng/ml ($p < 0.05$) (doubled)
		In 100 ml distilled	↑ TNF ($p < 0.05$), 4 fold increase by
	Results for *Undaria*	Water overnight, room temp, then Boiled for 60 min, filtered, 20-x dilution	monocytes = vs. control for proliferative respons of PBL

Author	Study	Groups	Biomarkers (treated vs. control)
Anastase-Ravion 2002	fucan A nodosum	**monocytes from human PB** Compared LPS +/- fucan	↑ IL-1α and TNF α when LPS and fucan together
			= IL-6
			↓ IL-8

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